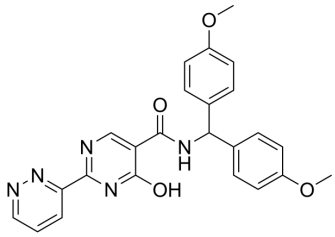
MK-8617

Cat. No.:	HY-101023
CAS No.:	1187990-87-9
Molecular Formula:	$C_{24}H_{21}N_5O_4$
Molecular Weight:	443.45
Target:	HIF/HIF Prolyl-Hydroxylase
Pathway:	Metabolic Enzyme/Protease
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 2 years -20°C 1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : 6 mg/mL (13.53 mM; Need ultrasonic)

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	2.2550 mL	11.2752 mL	22.5505 mL
	5 mM	0.4510 mL	2.2550 mL	4.5101 mL
	10 mM	0.2255 mL	1.1275 mL	2.2550 mL

Please refer to the solubility information to select the appropriate solvent.

BIOLOGICAL ACTIVITY

Description

MK-8617 is an orally active pan-inhibitor of hypoxia-inducible factor prolyl hydroxylase 1-3 (HIF PHD1-3) with an IC_{50} of 1 nM for PHD2.

IC_{50} & Target

IC50: 1 nM (PHD2)[1]

In Vitro

MK-8617 is an orally active pan-inhibitor of hypoxia-inducible factor prolyl hydroxylase 1-3 (HIF PHD1-3) with an IC_{50} of 1 nM for PHD2. MK-8617 is not a significant inhibitor of the cytochrome p450 enzymes in vitro (IC_{50}), CYP1A2, 3A4, 2B6, 2C9, 2C19, or 2D6, >60 μM, and is a moderate reversible inhibitor of CYP2C8 at 1.6 μM in vitro. The IC_{50} of MK-8617 is determined for factor inhibiting HIF (FIH) to be 18 μM[1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo

Tritiated MK-8617 exhibits minimal metabolic turnover in liver microsomes from rat, dog, and monkey (<10% turover) but significant turnover in human liver microsomes (34% turnover) after 60 min (10 μM MK-8617, 1 mg/mL microsomal protein). In terms of its pharmacokinetic profile, MK-8617 shows good oral bioavailability across species (36 to 71%), with low clearance and volume of distribution. After 48 h treatment of MK-8617, postdose recovery of the radioactivity is about 26%

	bile, 12% urine, and 38% in feces, indicating that ~38% of the MK-8617 is absorbed and eliminated into bile and urine which is consistent with the oral bioavailability (~36%) observed in the rat study. MK-8617 also elicits an increase in erythropoietin (EPO) levels with a mouse MED of 1.5 mpk when dosed iv[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	The catalytic activity assays for the HIF-PHD isoforms are performed at subsaturating levels of 2-oxoglutarate. To each well of a 96-well plate are added 1 µL of MK-8617 in DMSO and 20 µL of assay buffer containing 0.15 µg/mL FLAG-tagged full length HIF-PHD isoform expressed in and purified from baculovirus-infected Sf9 cells. After a 30 min preincubation at room temperature, the enzymatic reactions are initiated by the addition of 4 µL of substrates. After 2 h at room temperature, the reactions are terminated and signals are developed by the addition of a 25 µL quench/detection mix to a final concentration of 1 mM ortho-phenanthroline, 0.1 mM EDTA, 0.5 nM anti-$(His)_6$ LANCE reagent, 100 nM AF647-labeled streptavidin, and 2 µg/mL $(His)_6$-VHL complex. The ratio of time-resolved fluorescence signals at 665 and 620 nm is determined, and percent inhibition is calculated relative to an uninhibited control sample run in parallel[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Male Sprague-Dawley rats (approximately 300 g each, n=15/arm) are dosed once daily for 28 days with vehicle (25:75 v/v PEG200/water+1 mol equiv of NaOH) or MK-8617 (1.5 or 15 mg/kg in vehicle). A group of age-matched, untreated controls (n=15) are included in the experiment. On study days 3, 14, and 28, blood samples (~0.25 mL) are obtained via jugular venipuncture and on study day 36 by cardiocentesis for hematological and MK-8617 level analyses[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Drug Test Anal. 2022 Jul 19.
- Drug Test Anal. 2020 Aug 27.
- SSRN. 2023 Aug 15.

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REFERENCES

[1]. Debenham JS, et al. Discovery of N-[Bis(4-methoxyphenyl)methyl]-4-hydroxy-2-(pyridazin-3-yl)pyrimidine-5-carboxamide (MK-8617), an Orally Active Pan-Inhibitor of Hypoxia-Inducible Factor Prolyl Hydroxylase 1-3 (HIF PHD1-3) for the Treatment of Anemia. J Med Chem. 2016 Dec 22;59(24):11039-11049.

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